

**Military Infectious Diseases Research Program**  
**Licensed Products Information Papers**  
22 June 2005

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# What makes the Military Infectious Diseases Research Program (MIDRP) Unique?

*An overview of MIDRP efforts*



**Mission.** The mission of the Military Infectious Diseases Research Program (MIDRP) is to protect the U.S. military against naturally occurring infectious diseases via the development of FDA-approved drugs, vaccines and diagnostics, and EPA-approved vector control systems. Although the military has had notable successes in this undertaking, diseases such as malaria, dengue, diarrhea, and leishmaniasis continue to adversely impact military operations and the health of service members and their families.

**Objectives.** While the MIDRP shares some common research goals with other research organizations, the military has unique needs that are inadequately addressed by other Federal agencies, international programs and private industry. The goal of developing a malaria vaccine is one example. The focus of the international community is to develop a malaria vaccine that will prevent death in young children and pregnant women in areas of the world where malaria infections provide some natural immunity. MIDRP scientists actively support these efforts through multiple collaborations. However, the military needs a malaria vaccine that will protect service members with no prior natural immunity to avoid mission-degrading illness. Preventing death in children and keeping soldiers healthy and effective are distinct goals requiring different research strategies.

Until an effective malaria vaccine is available for military use, the military must continue to develop U.S. Food and Drug Administration (FDA)-approved drugs to treat malaria in service members. This needs to be a continuing effort because malaria parasites evolve mechanisms to resist the action of antimalarial agents, and the usefulness of any particular drug is time-limited. In contrast, the focus of international efforts is to provide already existing effective drugs (such as artemisinins) -- whether U.S. FDA approved or unapproved -- to prevent malaria-related deaths, particularly in Africa.

Other MIDRP objectives which are not addressed by other programs include development of:

- adenovirus vaccines to protect recruits in basic training from acute respiratory disease
- new, FDA-approved drugs to prevent malaria in non-immune service members (as opposed to development of drugs to treat malaria in persons residing in developing countries, where U.S. licensure and prophylactic drugs are not priorities)
- HIV/AIDS vaccines to protect the U.S. military against HIV strains found outside the U.S.



*"Because, if we fail to protect them, who will protect us?"*  
CDR Meg Ryan

- a second generation Japanese encephalitis vaccine to protect service members and others traveling to Asia, which will replace the vaccine being withdrawn from the market
- rapid diagnostic tests for leishmaniasis (one of many tropical diseases where there is little national interest outside of DoD)

Other MIDRP programs focus on scrub typhus, hemorrhagic fevers, and other deadly viruses found overseas. These are diseases of interest for DoD, but do not attract much research interest from other national research programs.

**Past Success.** The value of prophylactic drugs and vaccines to protect service members against infectious diseases has been obvious to the military since General George Washington inoculated his army to protect against smallpox. The U.S. military has been quite successful at creating vaccines and drugs. Since the passing of the 1962 Kefauver-Harris Drug Amendment, which requires medical products to be safe and efficacious, the military has been a partner in the development of seven different vaccines licensed in the U.S. (25 percent of all novel vaccines, and more than half the vaccines routinely given to protect our service members). Further, the military has contributed to the development of nearly all synthetic drugs licensed in the U.S. for the prevention and treatment of malaria (see separate MIDRP information paper, "An Overview of Licensed Products"). For decades, the DoD was the only federal agency developing new prophylactic and therapeutic drugs and vaccines for tropical diseases. However, today, an infectious disease threat anywhere in the world threatens the U.S. population at large. This natural biological threat has resulted in increased funding to other Federal agencies, but DoD infectious diseases research funding has decreased in real terms.

**Capabilities.** More than 300 MD and PhD level Army, Navy, Air Force, Government service civilian, and contract investigators lead MIDRP projects. These research professionals are stationed at major infectious diseases research laboratories in Maryland (The Walter Reed Army Institute of Research, The Naval Medical Research Center, and The United States Army Medical Research Institute of Infectious Diseases), and overseas (Peru, Egypt, Kenya, Thailand, and Indonesia with smaller detachments in Nepal, Uganda, Tanzania, Nigeria, Cameroon and Ghana). The U.S. military has stationed uniformed scientists in the tropics for more than 100 years, and with active overseas laboratories in place for as long as 58 years. Military scientists live and work in the tropics to study the disease threats in naturally affected populations. Countermeasures and candidate solutions are studied through all phases of development including field testing. These military scientists serve as goodwill ambassadors, and contribute to the development of health and science infrastructure in these tropical countries. Enduring relationships between tropical DoD facilities and ministries of health, international healthcare facilities, and local healthcare providers and researchers are of great value to the U.S. at a time when diseases such as SARS and avian influenza are potential global threats. The global MIDRP military presence provides a real-time early warning system in the identification and assessment of new and reemerging disease. Data from around the world is collected, analyzed, and immediately disseminated to military leadership and other agencies by the military's Global Emerging Infections System (GEIS).

The MIDRP is vertically integrated with full-spectrum capabilities that include basic science (enabling discovery and the knowledge base to solve problems encountered later in development), pre-clinical optimization, and advanced animal model development. Clinical trials expertise for early Phase 1 testing of drugs and vaccines through large (e.g. 42,000 volunteers for hepatitis A vaccine, and 62,000 volunteers for Japanese encephalitis vaccine) pivotal Phase 3 trials in developing nations is an especially valuable asset of the MIDRP. The DoD has high containment laboratories, pilot Good Manufacturing Practice (GMP) compliant bioproduction facilities, and FDA regulatory expertise in the U.S. and in many international settings.

As important as the talented researchers, modern facilities and sophisticated equipment is the MIDRP's proven capability to develop candidate products from basic science concepts through pilot scale manufacturing and all phases of animal and clinical evaluation. The program particularly excels at "translational research" to move a new product from the technology base to a level where a commercial partner will take the product on to licensure and marketing to the U.S. military and civilians. GlaxoSmithKline, Sanofi Pasteur, Barr Pharmaceuticals, Pfizer, and many other corporations have confidently

partnered with the DoD and provided the additional resources needed to get products to market. One of the MIDRP's major strengths is the recognition by industry collaborators of its neutrality in terms of lack of profit motive as it pursues its service mission. The trust that this engenders facilitates collaborations that could not otherwise be contemplated, allowing the sharing of trade secrets and the testing of many promising new technologies. These unique partnerships drive scientific discovery at a pace rarely achieved by the private sector.

The DoD receives approximately \$70 million of appropriated funds annually for infectious diseases research – less than 2 percent of the National Institutes of Health total spending on infectious diseases and immunology research. DoD maximizes the use of limited resources by partnering with other federal agencies, non-governmental organizations, and the pharmaceutical industry to focus on the unique infectious disease research and prevention needs of the U.S. military.

**What others think.** The following comments are extracted from two Institute of Medicine reports (Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance [2004]; and Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military [2002]).

*"The Walter Reed Army Institute of Research (WRAIR), through the United States Army Medical Research and Materiel Command (USAMRMC), is the leader in the United States for the development of new antimalarial drugs. Drug resistant malaria is considered a major military threat as well as an American public health issue. Military personnel, tourists, consultants, Peace Corps volunteers and State Department employees traveling to, or residing in, malaria endemic areas owe their safe travel to malaria endemic areas to the U.S. Military."*

*"Military scientists have a notable record of accomplishments when it comes to vaccines, including primary or significant roles in the development of vaccines against meningococcal meningitis, hepatitis A, Japanese encephalitis, and other dangerous infectious diseases. Partly because of the success of the DoD research programs, the public and even DoD nonmedical research personnel know little about them or the threats that their products have ameliorated."*

**For more information contact:**

COL David W. Vaughn, M.D., M.P.H.  
Director, Military Infectious Diseases Research Program  
504 Scott Street, MCMR-ZB-DRI  
Fort Detrick, MD 21702 Telephone: (301)619-7567  
Email: [david.vaughn@amedd.army.mil](mailto:david.vaughn@amedd.army.mil)

# Military Infectious Diseases Research Program (MIDRP)

*An overview of licensed products*



**Vaccines.** The discovery and development of vaccines to protect the warfighter is a priority for MIDRP. Vaccines can be administered prior to deployment, thereby obviating the need for prophylactic medication while protecting service members and reducing the medical logistic burden. Since the passing of the 1962 Kefauver-Harris Drug Amendment, which added the FDA requirement for proof of efficacy in addition to proof of safety for human products, there have been 28 innovative vaccines licensed in the U.S, including 13 vaccines currently designated for pediatric use. These 28 innovative vaccine products targeted new microorganisms, utilized new technology, or consisted of novel combinations of vaccines. Of these 28, the U.S. military played a significant role in the development of 7 licensed vaccines (25% of the total, or 40% if pediatric vaccines are excluded):

- Rubella (1969)
- Adenovirus 4 & 7 vaccines (1980)
- Tetravalent meningococcal vaccine (1981)
- Hepatitis B vaccine (1981)
- Oral typhoid vaccine (1989)
- Japanese encephalitis vaccine (1992)
- Hepatitis A vaccine (1995)

More than half of the routine vaccines given to service members were co-developed by the military.

Development of other licensed vaccines was supervised by investigators who began their careers at military research centers (e.g. yellow fever vaccine by former Army Surgeon General William Gorgas, mumps, measles, and varicella vaccines by Maurice Hilleman, and oral polio vaccine by Albert Sabin). Vaccines currently in advanced development stages include new adenovirus vaccines, and vaccines for malaria, dengue, and hepatitis E.

**Drugs.** MIDRP has contributed to the development of most synthetic drugs licensed in the United States for the prevention and treatment of malaria, including:

- Chloroquine (1949)
- Primaquine (1952)
- Sulfadoxine-pyrimethamine (1983)
- Mefloquine (1989)
- Doxycycline (1992)
- Halofantrine (1992)
- Atovaquone-Proguanil (2000)

Next generation antimalarial drugs include tafenoquine and an intravenous formulation of artesunate.

**Diagnostics and Vector Control.** MIDRP products include fieldworthy devices to diagnose human infections rapidly (such as scrub typhus), and to determine if insects are carrying infectious agents transmissible to humans (such as malaria parasites and West Nile Virus). Additional products include insect repellents and computer-based systems to identify potentially disease-carrying insects in the field.

## Other Contributions.

Licensed products reflect only a small portion of the contributions of the U.S. military to infectious diseases research. The U.S. military has been involved in the development of vaccines that serve as useful research tools, but were not licensed because of declining need. Examples include: (1) a 1945 multivalent polysaccharide pneumococcal vaccine (which showed benefits, but because of confidence in the newly

available drug penicillin, a vaccine was not licensed until 1977), and (2) the 1938 Cox vaccine to prevent louse-borne typhus used in World War II. Other contributions range from the demonstration that yellow fever was transmitted by a virus by Major Walter Reed in 1900 to the treatment of cholera by Captain R.A. Phillips in the 1940's (which led to development of oral rehydration solution) to the publication of the complete malaria genome in 2000. U.S. military physicians have authored and co-authored thousands of research publications elucidating the etiology, ecology, epidemiology and pathophysiology of many infectious diseases leading to effective treatment and control measures. Additionally, long-term deployment of military scientists to DoD laboratories in the tropics over the last 100 years has accelerated scientific discoveries and product development and accelerated technology transfer of research techniques and tropical disease control measures to developing countries.



# Influenza Vaccine

## Information Paper

*A licensed vaccine developed by DoD and its partner*

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product name:** Influenza virus vaccine

**Commercial name:** Influenza virus vaccine

**Date of U.S. licensure:** November 1945.

**Type of product:** Inactivated whole-virus vaccine,

**Company of manufacture:** Parke, Davis and Company, Detroit, Michigan

**Target Microorganism/associated disease:** Influenza viruses are comprised of 7-8 single-stranded RNA gene segments. The segmented nature of the genome permits reassortment of RNA between influenza viruses during dual infection, thereby creating forms of influenza unrecognized by the human immune system. Susceptibility to infection generally depends on host immunity. The major reservoir for influenza A in nature is aquatic fowl, although swine are susceptible to infection with influenza viruses from both birds and humans and may serve as a "mixing vessel" resulting in novel, disease-causing strains. Influenza A and B viruses are the principal causes of the epidemic influenza, although other respiratory viruses (including adenoviruses) can cause similar disease. Generalized symptoms, including fever, chills, muscle aches and headaches generally precede sore throat, nasal symptoms, hoarseness and cough. Death (in one-tenth of 1% of cases in most years) is limited to very young and very old persons. In pandemic years, larger proportions of young adults have died following an abbreviated course of illness sometimes marked by cyanosis and bloody sputum.

**Reasons for development:** Approximately one out of every 67 soldiers died of influenza during the influenza pandemic of 1918-1919. Furthermore, the close quartering and transport of large numbers of military members across oceans may have contributed to rapid spread of influenza globally during 1918-1919. If it had not been for the influenza pandemic, World War I would have been the first war when more people died of battlefield injuries than disease (but the U.S. Army lost a greater proportion of men to death by disease in 1918 than in any year since 1867).

### **Role of Department of Defense in product**

**development:** Influenza vaccine was developed to protect service members and civilians from sickness and death due to influenza. During the First World War, U.S. Army Surgeon General Gorgas developed a series of Commissions to gather the best civilian and military input on ongoing and recurring infectious disease problems. In the spring of 1918, a Pneumonia Commission was formed to study the unusually high numbers of complicated pneumonias and pleurisy occurring in the European



*Seattle policemen wear masks to guard against the 1918 flu pandemic, which killed more Americans than did World War I. Photo from American Museum of Natural History website.*

Theatre. Several Commissions continued during the interwar years. The Army established the Board for the Investigation and Control of Influenza and other epidemic diseases in 1941, which later became the Army Epidemiology Board and eventually the Armed Forces Epidemiology Board (in 1949). Influenza vaccine viral strains used to make the Parke, Davis and Company influenza vaccine were obtained from Dr. Thomas Francis, Jr., Commission on Influenza, U.S. Army, School of Public Health, University of Michigan, Ann Arbor, Michigan. (Dr. Francis is accredited with first isolating influenza B.) This inactivated vaccine was studied in military recruits and college students. (The live-attenuated influenza vaccine licensed in 2003 also originated from this University of Michigan laboratory).

DoD has also funded studies investigating the transmission and prevention of influenza in military populations. In 1976, an outbreak of influenza on a military post caused by influenza similar to the causative agent of the 1918-1919 pandemic resulted in an effort to immunize the entire population of the United States. Because of reports of Guillain-Barre syndrome (GBS) in civilian (but not military) recipients of influenza vaccine, the immunization effort was terminated. Between 1961 and 1993, the AFEB made 53 separate recommendations regarding the composition of influenza vaccines. More recently, the Assistant Secretary of Defense (Health Affairs) has issued several policy statements per year guiding the DOD in influenza, management, and DOD representatives often participate in the FDA Advisory Committee that reviews influenza-related products.

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# Rubella Vaccine

## Information Paper

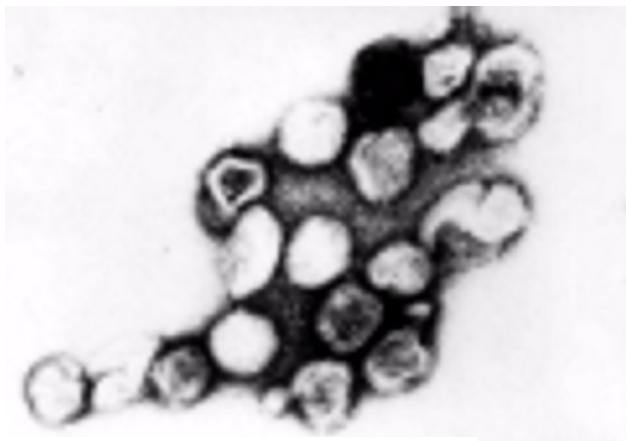
*A licensed vaccine developed by DoD and its partners*

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product Name:** Rubella Vaccine  
**Commercial Name:** Meruvax (now Meruvax II)  
**Date of U.S. Licensure:** 1969  
**Type of Product:** live-attenuated viral vaccine  
**Company of Manufacture:** Merck Sharp & Dohme

**Target Microorganism/Associated Disease:** German researchers first identified the disease "German measles" -- later known as "rubella" from the Latin "rubellus" meaning "reddish" -- as distinct from measles in 1814. Rubella is caused by a single-stranded RNA virus which spreads person-to-person (humans are the only known host) via respiratory droplets. The rubella virus causes fever and rash, which is followed by long-term joint pain and inflammation in rare cases. However, in early gestation rubella infection can result in serious fetal malformations (hearing impairments, heart defects/inflammation, mental retardation, brain inflammation, enlargement of the spleen and liver, low blood platelets).



*Transmission electron micrograph of rubella virus*

**Reasons for Development:** Prior to 1969, military recruits and military hospital workers (particularly females of childbearing age) were at risk for rubella infection. Beginning in 1947, pregnant women exposed to rubella were given convalescent serum or immune serum globulin to prevent fetal infection. A rubella pandemic that hit Europe in 1962, then caused 12.5 million cases of rubella and 2,000 cases of rubella encephalitis in the U.S. from 1963-4, with 30,000 afflicted infants (1% of all pregnancies, with 6,250 spontaneous abortions and 2,100 excess neonatal deaths) prompted rubella vaccine efforts.



*Infant with congenital rubella syndrome*

### **Role of Department of Defense in Vaccine**

**Development:** In 1962, COL Edward Buescher, COL Malcolm Artenstein, and CPT Paul Parkman of the Walter Reed Army Institute of Research (WRAIR) isolated the rubella virus from a recruit hospitalized at Fort Dix during an adenovirus outbreak investigation using virological techniques pioneered by scientists at WRAIR. (Weller and Neva also isolated the rubella virus at Harvard University in 1962). Parkman then moved on to the Food and Drug Administration, where, together with Dr. Harry Meyer, he used the isolated HPV-77 virus grown in duck-embryo culture to create Meruvax, (Merck)-- one of three rubella vaccines licensed in the U.S. in 1969. (A different viral strain [RA 27/3] was used as the basis of Meruvax II beginning in 1979.) Dr. Stanley Plotkin, a research physician at the Wistar Institute in Philadelphia, developed the RA 27/3 rubella strain (isolated from a fetus legally aborted in 1965) which became part of the Measles, Mumps and Rubella live virus vaccine II (MMRII, licensed in the U.S. in 1979, and recommended as a preferred agent for U.S. children in 1980). The impact of the rubella vaccine has been dramatic. During the 3 years before the vaccine was brought to market in 1969, 47,745 cases of rubella were recorded in the U.S.; as of 2005, rubella virus infection has been eliminated in the U.S.

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# Adenovirus Vaccine

## Information Paper

*A licensed vaccine developed by DoD and its partners*



**Product name:** Adenovirus vaccine

**Commercial name:**

Adenovirus Vaccine live oral type 4

Adenovirus Vaccine live oral type 7

**Date of U.S. licensure:** 1980 (out of production 1995; not available after 1998 [adenovirus 4 vaccine] and 1999 [adenovirus 7 vaccine]).

**Type of product:** live viral vaccine tablet for oral administration

**Company of manufacture:** Wyeth (1980-1995)

**Target microorganism/associated disease:**

Adenoviruses are DNA viruses that are usually transmitted via respiratory (aggravated by crowding) or ocular (spread via swimming pools, physician offices with inadequate sterilization and handwashing practices) routes. Asymptomatic infection and a prolonged carrier state contribute to spread. Diseases associated with adenoviral infections include febrile respiratory illness (bronchitis or pneumonia), eye infections (conjunctivitis), sore throat, and diarrhea. Complications of adenovirus include acute bacterial ear and lung infections, and death.

**Reasons for development:** Adenovirus -- a frequent cause of epidemic acute respiratory disease (ARD) associated with pneumonia, hospitalizations and some deaths especially among military recruits -- is a proven threat to military readiness. Adenovirus infections also cause illness among deployed troops and civilians. There is no effective antiviral treatment for adenovirus. During World War II, epidemics of respiratory disease in new recruits disrupted training and greatly increased the burden on medical staff and facilities. Before vaccines were available, adenovirus was consistently isolated in 30-70% of trainees with ARD, and adenoviruses were associated with 90% of the cases of pneumonia among trainees in basic combat training (BCT). The vast majority of all adenovirus infections in BCT are caused by serotypes 4 and 7. In prospective studies in the 1950's of ARD in BCT recruits, Hilleman and his co-workers established that 20% of recruits were hospitalized with febrile ARD, another 20% sought evaluation at an outpatient facility, 40% had mild or inapparent infections, and the remaining 20% (probably immune) were not infected. In a similar subsequent study of an ARD outbreak in BCT recruits at Fort Dix in the 1960s, Buescher and his co-workers observed that 37% were hospitalized with febrile ARD, and an additional 48% were also ill with less severe infections. Since termination of Wyeth vaccine production in 1995, the burden of adenovirus disease in recruits has increased to that of the pre-vaccine era.



*Massive congestion and focal necrosis are seen in the left lung. Adenovirus was proven from the lung tissue obtained at autopsy. Photo from [www.yamagiku.co.jp/pathology/image/093/1.jpg](http://www.yamagiku.co.jp/pathology/image/093/1.jpg).*

**Role of Department of Defense in product**

**development:** A commission on ARD was established at FT Bragg, NC from 1942 to 1945 to undertake epidemiologic studies. The viral nature of these infections was established when bacteria-free filtrates were shown to transmit the infection to volunteers. In the 1950s, Hilleman and Werner at the Walter Reed Army Institute of Research (WRAIR) identified adenovirus types 4 and 7, and established the importance of neutralizing antibody as a marker of immunity for these infections. Effective formalin-inactivated type 4 and 7 vaccines were developed in the 1950's and licensed by the FDA but subsequently withdrawn because of variable potency and concerns (later established as unfounded) regarding potential oncogenicity due to contamination with SV-40. Because ARD epidemics caused by adenovirus type 7 continued, Top and co-workers at WRAIR developed a similar safe, highly antigenic live oral adenovirus type 7 vaccine. After extensive testing, these vaccines were approved for distribution by Wyeth Laboratories in 1980. The Wyeth adenovirus vaccines were effective in preventing ARD in recruits without producing adverse effects. In 1995, Wyeth -- the sole manufacturer of adenovirus vaccines -- elected to cease production when faced with the requirement for costly updated manufacturing facilities for the vaccine; DoD supplies were depleted by 1999. Because of the subsequent surge of adenovirus cases in recruits, DoD contracted with Barr Laboratories in September 2001 to develop replacement live adenovirus vaccines. The first clinical study of the new adenovirus types 4 and 7 vaccines has been successfully completed by investigators at Fort Sam Houston.

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# Meningococcal Vaccine

## Information Paper

*A licensed vaccine developed by DoD and its partners*

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product name:** Meningococcal vaccine

**Commercial name:** MENOMUNE

**Date of U.S. licensure:** A, C, Y, W-135, tetravalent vaccine licensed November 1981

**Type of product:** purified capsular polysaccharide bacterial vaccine

**Company of manufacture:** Connaught

**Target microorganism/associated disease:** *Neisseria meningitidis* is a gram-negative bacterium with the microscopic appearance of two kidney beans aligned along their long axis. The bacteria are encapsulated by a polysaccharide coat, which contains important determinant of potential virulence. Five antigenically distinct capsular polysaccharide serogroups, designated groups A, B, C, Y, and W-135, account for almost all human disease, although 13 groups have been identified. The bacteria are transmitted via infected respiratory droplets under conditions favoring close person-to-person contact. Humans serve as the only host and reservoir for *N. meningitidis* infections. After an incubation period of 2-10 days, the bacteria may either harmlessly colonize the human nasopharynx, or become invasive pathogens causing life-threatening (10-30% case-fatality rate) bacterial meningitis and sepsis.

Whether a given meningococcal infection will result in an asymptomatic carrier state or in a devastating systemic disease depends on host immunity, bacterial virulence and other factors (lack of a spleen, cigarette smoking, viral upper respiratory infections and alcohol consumption are associated with increased risk of disease). Infections with *N. meningitidis* bacteria occur globally. Large-scale epidemics afflict Africa particularly in the sub-Saharan region during the dry season. The risk of meningococcal disease transmission to pilgrims on the hajj pilgrimage to Mecca in Saudi Arabia (and subsequent contacts of the pilgrims) has been recognized for decades. Meningococcal infections cause significant morbidity among pediatric populations, with the highest incidence in children under the age of 5 years, but there is a second peak in disease incidence among teenagers and young adults.

**Reason for development:** Outbreaks of meningococcal disease among military recruits and soldiers have been documented since the early 19th century, although the etiology was not recognized until later. Increased risks of meningococcal infections are associated with close exposures to large populations of persons from diverse geographic areas that are under stress. During the period from 1964 to 1971, coincident with the Vietnam War, an epidemic of group B and group C meningococcal disease occurred in U.S. military basic training centers. Approximately 2400 cases occurred in active duty military

*Meningitis is an acute bacterial disease characterized by sudden fever, headache, nausea and rash. Delirium and coma are followed by death in about 15% of cases. In the 1960's more than 300 cases per year occurred in Army recruits with about 10% mortality.*



personnel annually with a case-fatality rate of about 7.2% (about 170 deaths). This epidemic and the loss of sulfadiazine as an effective prophylactic agent (due to outbreak strain resistance) led to an intensive effort at the Walter Reed Army Institute of Research (WRAIR) to develop a vaccine to protect military personnel.

**Role of DoD in product development:** Beginning in 1963, a team of investigators, led by Malcolm Artenstein, Emil Gotschlich, and Irving Goldschneider conducted studies over a 5 year period that elucidated the human immunologic response to meningococcus, including the concept that circulating antibody prevented clinical disease, and provided a basis for the successful development of effective polysaccharide vaccines for serogroups A and C. WRAIR created the first subunit vaccine; this C vaccine began to be used for routine vaccination of recruits entering basic training in 1970, and was replaced by an A/C divalent vaccine in 1978. The team's contributions included development of methods for purification of high molecular weight polysaccharides from groups A, B, and C; physical and chemical analysis of the polysaccharides; immunogenicity studies in several animal species; production of clinical grade vaccine; and Phase 1, Phase 2 and Phase 3 clinical trials which demonstrated high efficacy and culminated in the licensure of the vaccine.

Work on the development of vaccines for serogroups Y and W135 and testing of a tetravalent A, C, Y, W135 vaccine took place independently at several institutions including Connaught Laboratories, Inc., WRAIR, Institut Merieux, and the Rixensart, Belgium branch of Smith-Kline between 1975 and 1981. The group Y and W135 capsular polysaccharides were purified and characterized by these different institutions using the same methods developed at the WRAIR for the group C and A vaccines. The licensure of the tetravalent vaccine by Connaught Laboratories Inc. in 1981 was based on the company's own clinical data. Group B meningococcal vaccine is currently under development at WRAIR.

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# Hepatitis B Vaccine

## Information Paper

*A licensed vaccine developed by DoD and its partners*



**Product name:** Hepatitis B Vaccine  
**Commercial name:** Hepatavax B  
**Date of U.S. licensure:** 1981  
**Company of manufacture:** Merck Sharp and Dohme

**Type of product:** This first-generation vaccine was prepared from 22nM HBsAg particles purified from plasma donations from chronic HBV carriers. These preparations are safe and immunogenic, but have been replaced in most countries by recombinant vaccines produced by the expression of recombinant HBsAg in yeast cells.

**Target microorganism/associated disease:** Hepatitis B virus (HBV) is transmitted by blood-to-blood and sexual contact and is an important cause of acute and chronic viral infection of the liver in many countries. The clinical features of acute hepatitis B infection resemble those caused by other viral hepatitis viruses. The HBV virus persists in approximately 5-10% of healthy adults, and in as many as 90% of infants infected at birth. Persistent carriage of hepatitis B, defined by the presence of hepatitis B surface antigen (HBsAg) in serum for more than 6 months, has been estimated to affect about 350 million people worldwide, although not all carriers can transmit the virus to others. Long-term continuing HBV replication can result in chronic liver disease, cirrhosis, and hepatocellular carcinoma, and results in 1-2 million deaths per year. Primary liver cancer is one of the 10 most common cancers worldwide, and currently 80% of such cancers are ascribed to persistent infection with HBV.

**Reason for development:** Soldiers are at risk for exposure to HBV-contaminated blood and body fluids during battle (and sexual intercourse). Acute hepatitis was one of the main causes of illness among military members during the Vietnam war. A significant part of this was probably a consequence of contaminated needle use. Some service members from Vietnam and other wars continue injected drug use after returning to the U.S., and remained at risk from hepatitis B from shared needles.

**Role of Department of Defense in product development:** The U.S. military became focused on hepatitis B after the summer of 1942, when 50,000 cases of jaundice and 62 deaths occurred among soldiers vaccinated with the yellow fever vaccine. Investigators attributed the illness to a virus transmitted from human serum used in vaccine manufacture. The epidemic ceased after suspect vaccine lots were destroyed, and a human

serum-free process was utilized. Investigations of stored samples many years later confirmed that the causative agent was HBV.

Beginning in 1944 and continuing through the 1970's, the U.S. Army Surgeon

General's office supported studies at Yale University and the Willowbrook State Hospital in New York which characterized the epidemiology and required immunoprophylaxis for two different viral causes of epidemic hepatitis, including hepatitis B. Following Blumberg's discovery of the Australia antigen (HAA; now known as HBsAg) in 1965, the association of this antigen with hepatitis B was recognized, which made possible additional epidemiologic studies linking hepatitis B with intravenous drug abuse and sexual exposure.



*This woman is suffering from liver cancer caused by hepatitis B.*

In the late 1960s, scientists at the U.S. Army Medical Research Laboratory at Fort Knox, Kentucky collaborated in a study of more than 1600 members of the Armored Brigade; the cohort included both soldiers who had recently returned from Vietnam and recruits who had not yet been to Southeast Asia. A significantly higher frequency of HBsAg carriers among the returnees (about 0.7%) than among the recruits (0.2%) was noted. In the early 1970s a second larger study involving nearly 20,000 Vietnam War returnees and recruits was initiated, which also incorporated data from returnees participating in a drug rehabilitation program. The higher HBsAg rate among newly returned service members was attributed to HBV acquired via injected drug use, but some returnees initially testing positive eventually became HBsAg negative due to presumed recovery from HBV.

Current HBV vaccines utilize subtype "adw". Investigators at the Walter Reed Army Institute of Research carried out early work on subtyping strains of HBsAg from different geographic regions, and first described the w" and "r" antigenic determinants.

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# Typhoid Vaccine

## Information Paper

*A licensed vaccine developed by DoD and its partners*



**Product name:** Oral live typhoid vaccine

**Commercial name:** Vivotif Berna

**Date of licensure:** December 1989

**Type of product:** attenuated live oral enteric-coated vaccine based on Ty21A strain

**Company of manufacture:** Berna Products (now Acambis)

**Target microorganism/associated disease:** Typhoid fever, an acute generalized illness caused by infection with the bacterium commonly referred to as *Salmonella typhi*, is characterized by fever, headache, abdominal pain, mild rash, and bowel movement and mental changes. The word "typhoid" is derived from the Greek "typhos", which means "smoke" because the disease is associated with mental confusion. *Salmonella typhi*, which causes infection only in humans, is acquired by ingestion of contaminated food or water or finger-to-mouth contact with contaminated feces. The infection can be spread by a healthy carrier of the bacterium ("typhoid Mary"). Typhoid fever is primarily a disease of adolescents and young adults, and may be fatal in untreated susceptible persons.

**Reasons for development:** During the Spanish-American War, one-fifth of U.S. troops (mostly U.S. Army) had typhoid fever, and over 1500 persons died of the disease. In the Anglo-Boer War the British army lost more men to typhoid (8225 deaths) than it did to wounds (7582 deaths). Development of a typhoid vaccine became a priority for both nations.

**Role of Department of Defense in product development:** Observational studies dating back to the Civil War had revealed that some typhoid fever survivors were not susceptible to repeat bouts of this illness. This evidence of natural immunity prompted efforts to develop vaccines to prevent typhoid fever. The first typhoid vaccines were created in Britain in 1896 by Wright; Leishman then created a more potent and less toxic version. After Captain Frederic Russell of the U.S. Army modified Leishman's vaccine to create a subcutaneous form and conducted volunteer studies demonstrating safety and efficacy, typhoid immunization was required of

all U.S. service members beginning 30 September 1911. The U.S. Army became the first military organization in the world to make typhoid vaccination mandatory, and had the lowest typhoid fever incidence of any major combatant in World War I. The first typhoid vaccine was licensed in the U.S. in 1914.

Levine and others conducted large scale studies in the 1980's in collaboration with the Ministry of Health in Chile with DoD funding which demonstrated 67% efficacy of an enteric-coated form of an attenuated Ty21a strain of *S. typhi* in conditions of moderate typhoid fever transmission in Chile. Later that decade, Simanjuntak and others at the Naval Medical Research Unit in Jakarta (NAMRU-2) and the Indonesian Ministry of Health demonstrated 42% efficacy of this vaccine in a setting of intense transmission of typhoid fever in Jakarta. The licensed version of Ty21A (Vivotif Berna) -- four enteric-coated capsules taken every other day -- helps protect against the disease, but other preventive measures such as hygiene are advised (as is the case with all typhoid vaccines, whether given by mouth or by injection).

The U.S. military has contributed to control of typhoid fever in other ways. (1) Identification of pathological bowel findings (such as enlarged intestinal lymphoid follicles or "Peyer's patches") during autopsies by U.S. Civil War surgeons were eventually linked to typhoid infection. (2) In 1899, during the Spanish-American War, the Reed-Vaughan-Shakespeare Typhoid Board was established. This board, with Major Walter Reed, Major Victor C. Vaughan, and Major Edward O. Shakespeare, carried out epidemiological investigations focusing on typhoid fever and noted that (1) either sick or healthy human carriers of typhoid bacilli were important sources of typhoid infection; and (2) the U.S. Army had failed to undertake established sanitary measures to prevent typhoid fever during the Spanish-American War. MAJ Carl Darnall developed a method of water purification in 1910, and MAJ William Lyster developed a water purification system using calcium hypochlorite in a linen bag (Lyster bag) in 1915.

The U.S. military has also contributed to improved treatments for typhoid fever patients. In 1948, Joseph Swadel, Ted Woodward, Herb Ley and Charles Wissman of The Walter Reed Army Institute of Research noted a patient given chloramphenicol for scrub typhus had typhoid fever responsive to chloramphenicol. Subsequently, investigators at NAMRU-2 and NAMRU-3 have demonstrated the utility of other antimicrobial agents for typhoid fever. Stephen Hoffman and others revealed the usefulness of dexamethasone in reducing mortality from severe typhoid fever in 1984.



*Typhoid fever remains a problem in countries that lack clean water and well-functioning sanitation systems.*

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# Japanese Encephalitis Vaccine Information Paper

*A licensed vaccine developed by DoD and its partners*



**Product name:** Japanese Encephalitis Vaccine  
**Commercial name:** JE-Vax  
**Date of U.S. licensure:** 10 December 1992  
**Type of product:** formalin-inactivated whole virus  
**Company of manufacture:** The Research Foundation for Microbial Diseases of Osaka University (BIKEN), currently distributed in the United States by sanofi-pasteur

**Target microorganism/associated disease:** Japanese encephalitis virus (JEV; previously called Japanese encephalitis type B) is a flavivirus transmitted by mosquitoes that is associated with outbreaks of encephalitis (brain inflammation) in Asia, the Pacific Islands, northern Australia and Russia. JEV transmission is generally seasonal and limited to rural areas (pigs and birds are important for viral maintenance, amplification and spread). Within Asia, Japanese encephalitis (JE) is the most important cause of human encephalitis, and causes approximately 35,000 cases and 10,000 deaths annually. Although between 25 and 1,000 asymptomatic JEV infections occur for each identified clinical case of JE, and symptoms may be limited to mild illness with fever in some persons, the case-fatality rate for persons with evident disease is about 25%, and at least 50% of JE survivors have sequelae ranging from mood changes to severe neurological impairment.

**Reasons for development:** The first Japanese encephalitis vaccine utilized by U.S. forces was developed during WWII to protect U.S. troops deployed to Asia and the Pacific. Outbreaks of JE occurred among U.S. troops in Okinawa in 1945. A need for a more efficacious vaccine became apparent during U.S. involvement in the Korean War, when there were 299 cases of proven or suspected JE among US forces despite administration of JE vaccine to all U.S. troops in the Far East Command between 1946 and 1951 (at which point the U.S. army ceased JE vaccine administration). Currently, there is no effective treatment of JE beyond supportive care, and use of pesticides results in minor reductions of JEV vectors in a limited area for a short period of time at considerable cost.

**Role of Department of Defense in product development:** JEV was first isolated in 1935 from the brain of a patient dying of encephalitis in Japan. At the beginning of World War II, anticipating possible epidemics among U.S. forces in the Pacific, the Commission on Neurotropic Virus Diseases of the Army Epidemiology Board assigned MAJ. Albert Sabin the task of developing a vaccine against JE and to stockpile vaccine to be used in the event of outbreaks. A crude vaccine derived from formalin-inactivated brains of



*Child with JEV in Children's Hospital, Bangkok, Thailand.*

mice infected with JEV was developed (based on the earlier work of Japanese and Russian scientists) and administered to approximately 250,000 military personnel during World War II, beginning shortly after the outbreak in Okinawa. In addition, Sabin and others recorded clinical descriptions of laboratory-confirmed cases, and performed studies to identify the natural vectors and reservoirs.

The ecology of JEV was elucidated in greater detail by Walter Reed Army Institute of Research investigators Buescher and Scherer working in Japan in the late 1950's. Increased demand for a JEV vaccine for U.S. citizens began in 1981, when a 20-year-old student from Washington, D.C. contracted fatal JE at Beijing University. Japanese encephalitis vaccine trials were conducted by the U.S. Centers for Disease Control (CDC) beginning in 1983, when the CDC began distributing the vaccine in the U.S. under an Investigational New Drug application until 1987. An initial 3-dose regimen (plus booster doses) is recommended by the CDC for optimal immune response.

In the mid-1980's, DoD led by Charles Hoke with collaborators in the Thai Ministry of Public Health conducted the definitive study evaluating 2 doses (given 1 week apart) of the highly purified BIKEN vaccine (Nakayama-Yoken strain) versus a bivalent vaccine (NakayamaYoken and Beijing-1 strains) versus placebo (tetanus toxoid). There were approximately 22,000 Thai schoolchildren in each of these recipient groups. The efficacy of both monovalent and bivalent vaccines was 91 percent, achieved with minor vaccine adverse effects (headache, sore arm, rash, and swelling), and this data was pivotal in obtaining FDA licensure.

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# Hepatitis A Vaccine

## Information Paper

*A licensed vaccine developed by DoD and its partners*

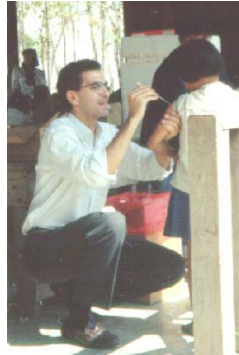


**Product name:** Hepatitis A Vaccine  
**Commercial name:** HAVRIX  
**Date of U.S. licensure:** February 1995  
**Type of product:** Inactivated viral vaccine  
**Company of manufacture:** SmithKline Beecham

**Target microorganism/associated disease:** Hepatitis A virus (HAV) a non-enveloped, single-stranded RNA virus is endemic in most tropical and subtropical regions of the world. The virus is transmitted when food or water becomes contaminated with feces of infected persons. In developing nations, the virus is generally acquired early in life and rarely causes severe symptoms. In developed nations with better sanitation, infection with hepatitis A may be delayed until an individual travels to an underdeveloped area, or there is an unusual breakdown in sanitation. Infections in adults may be associated with serious symptoms and rare fatalities.

**Reasons for development:** Epidemics of hepatitis A have repeatedly afflicted the US military during deployments to regions with suboptimal sanitation, water, and waste systems. During the Civil War, epidemic hepatitis, (most likely due to hepatitis A virus) was common, but few deaths were recorded. During the second year of the war, about 50 of every 1,000 men became jaundiced; only about half this number were diagnosed in subsequent years. While improved sanitation may have contributed slightly to the decrease, it is more likely that veteran soldiers were eventually exposed to the disease and acquired immunity. In World War I, hepatitis was a serious problem for British, French and German troops, but less of a problem for U.S. troops. U.S. forces experienced greater than 180,000 cases of infectious hepatitis in World War II, with 106,695 admissions, and a case-fatality ratio of 0.3%. The annual admission rate per 1000 was 4.37 overall, with the highest rates of disease in the Southwest Pacific and the Mediterranean. In the Korean War, an outbreak of hepatitis occurred when both American and Korean soldiers were crowded into the Pusan perimeter. In the autumn and winter of 1950, 4,000 patients with hepatitis were hospitalized.

Outbreaks of hepatitis A disease have afflicted the military during peacetime. In 1959, uncooked fish was implicated in an outbreak in Naples involving 156 persons on 14 ships. In 1974, a food handler in San Diego was suspected of causing a large number of cases (47/1000 attack rate) in San Diego. In 1980, child care centers were recognized as a focus for hepatitis A transmission on military posts.



*LTC Bruce Innis led the Phase 3 HAV vaccine trial with Thai collaborators.*

Immune serum globulin (ISG), previously used to protect soldiers and travelers from infection with hepatitis A, requires repeated injections, and is not readily available. Also, with large and lengthy deployments, distribution of ISG has proved impractical and unpopular.

**Role of Department of Defense in product development:** Much of the HAV product development is attributable to the U.S. military in partnership with the National Institutes of Health (NIH) and SmithKline Beecham (SKB, now GlaxoSmithKline Biologicals). Techniques to quantify hepatitis A virus and associated antibodies were developed at the Walter Reed Army Institute of Research (WRAIR). At the WRAIR and NIH (laboratory of Dr. Robert Purcell) numerous cell types were evaluated for their ability to support growth of hepatitis A virus, and optimal growth parameters were defined. Both guinea pigs and monkeys developed excellent titers of neutralizing antibody following immunization with a prototype formalin-inactivated vaccine created by Binn, Dubois and Eckels. Analysis of strains from international sources showed antigenic similarity, and indicated that a vaccine need contain only a single serotype to provide global protection against HAV. Human trials began at WRAIR in 1986 with formalin-inactivated vaccine; all eight volunteers developed neutralizing antibody after four small doses of vaccine antigen. The DoD established cooperative agreements with SKB for hepatitis A vaccine development in 1989. Initial small-scale collaborative investigations evaluated antibody responses in humans following immunization with two candidate vaccine strains. A 1991 study of co-administration of hepatitis A vaccine with hepatitis B vaccine to soldiers did not alter results for either vaccine. Another 1991 study showed that accelerated hepatitis A immunization schedules were effective for soldiers. A large-scale field efficacy trial of hepatitis A vaccine (showing 94% efficacy) was begun in 1991 as a collaborative project of the U.S. Army and the Ministry of Health of Thailand. (Because of improving sanitation, rates of transmission were lower than had been anticipated and a large study was required.) In this trial, approximately 20,000 volunteers received hepatitis A vaccine and 20,000 received placebo (hepatitis B vaccine).

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# Chloroquine Information Paper

A licensed antimalarial drug developed by DoD & its partners

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product name:** Chloroquine

**Commercial name:** Aralen

**Application:** Antimalarial drug for treatment and prevention of malaria

**Date of U.S. licensure:** October 1949

**Type of product:** 4-aminoquinoline

**Company of manufacture:** Multiple pharmaceutical companies were involved in the development of this drug, including Winthrop, Abbott, E.R. Squibb and Sons, Eli Lilly and Company, Sharp and Dohmne, Inc. The drug is currently manufactured by Sanofi Synthelabo.

Quinine, derived from the bark of the cinchona tree, has been a mainstay of malaria treatment for hundreds of years. The drug is very effective for some types of malaria -- especially when combined with other antimalarial drugs -- but adverse effects (referred to as "cinchonism" and a short duration of action render it an imperfect prophylactic agents. The World Wars prompted an effort to develop synthetic drugs to prevent and treat malaria because of quinine supply problems and the need for long-acting prophylactic drugs to prevent malaria in troops. During World War I, countries producing quinine were controlled by Allied forces, which led to initial efforts by German companies to synthesize antimalarial compounds. But because pharmaceutical development requires many years, such drugs were not developed until after World War I. The earliest work in synthesizing antimalarial drugs was based on the work of a German scientist named Paul Ehrlich. While studying the newly discovered aniline dyes to develop methods for staining human tissues in 1891, he observed that the dye methylene blue stained malaria parasites, and that malaria organisms did not survive after ingesting large amounts of this dye. Dr. Ehrlich cured two patients of malaria using methylene blue -- the first time a synthetic drug was used to treat humans.

Bayer, one of the leading German dye companies, soon became a leading pharmaceutical company. A team of chemists and biologists was assembled by Bayer to develop new synthetic antimalarials using methylene blue as a prototype. In 1930 German scientists synthesized another antimalarial compound based on a known dye (9-amino acridine, later known as atabrine). Although U.S. service members in Panama were involved in some clinical trials to test the efficacy of this drug, Germany controlled atabrine manufacturing until U.S. scientists succeeded in initiating the manufacture of atabrine in 1941.

The Allied push to synthesize antimalarial agents during World War II -- spearheaded by the U.S. military-- was prompted by the Japanese seizure of Java (which then supplied 90% of the world's supply of quinine). Concerns about adverse effects of atabrine (yellowing of the skin, and Japanese propaganda suggesting the drug caused



*"Doctor, this will be a long war if for every division I have facing the enemy I must count on a second division in the hospital with malaria and a third division convalescing from this debilitating disease!"*  
GEN Douglas MacArthur - May 1943"

impotence) led to noncompliance. After dosing studies were undertaken with U.S. soldiers at Fort Knox, and Neil Fairly (an Australian military physician) showed that placing volunteer Australian troops on a daily atabrine regime was effective in preventing malaria, atabrine prophylaxis was rigidly imposed on Allied forces operating in malarious areas. Control of malaria was an important factor in Allied success in World War II.

Allied interest in chloroquine followed the capture of German supplies of a structural analog called ontoquine in Tunis in 1943. Both chloroquine and ontoquine had been patented in the U.S in 1941 by the Winthrop Company, which had a cartel agreement with IG Farbenindustrie, the original manufacturer of these compounds, but drug development had stalled. Chloroquine rapidly controlled clinical symptoms of susceptible *P. falciparum* and *P. vivax* malaria with minimal toxicity, and was also useful as a once-weekly prophylactic drug.

In the 1950's Mario Pinotti in Brazil introduced the strategy of putting chloroquine into common cooking salt as a way of distributing the drug as a prophylactic on a wide scale. This medicated salt program became known as "Pinotti's method" and was employed in South America as well as parts of Africa and Asia. Chloroquine, along with widespread use of the residual insecticide DDT, was a major component of the WHO Global Eradication Programme of the 1950's and 1960's. Chloroquine has been safely used in pregnant women and children. However, the emergence of chloroquine-resistant *P. falciparum* and *P. vivax* have rendered this drug less useful. Chloroquine has also proved useful as a treatment for connective tissue disorders.

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Greenwood D. Conflicts of interest: the genesis of synthetic antimalarial agents in peace and war. *Journal of Antimicrobial Chemotherapy* 1995;36:857-872.

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[www.CDC.gov/malaria/history](http://www.CDC.gov/malaria/history)

# Primaquine Information Paper

A licensed antimalarial drug developed by DoD and its partners

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product name:** Primaquine

**Commercial name:** Primaquine

**Application:** Anti-malarial drug for treatment and prevention of relapsing malaria

**Date of U.S. licensure:** January 1952 (for military use only); August 1952 (for all persons, including civilians)

**Type of product:** 8 aminoquinoline oral drug

**Company of manufacture:** Winthrop-Stearns, Inc.

**Reasons for development:** Relapsing malaria due primarily to *P. vivax* afflicted U.S. service members during World War II and the Korean War. These relapses are associated with release of latent forms of parasites from the liver following *P. vivax* and *P. ovale* infections.

## Role of DoD:

Primaquine is derived from methylene blue and is a close structural analog of pamaquine, the first synthetic antimalarial agent produced in Germany in 1926, which was too toxic for clinical use. Primaquine (synthesized by Dr. Robert C. Elderfield of Columbia University) was developed by the U.S. Army during World War II beginning in 1944, when malaria (some of it relapsing illness due to *P. vivax*) was a serious burden to U.S. troops in the Pacific and India-Burma theaters. The 8-aminoquinoline group of antimalarials demonstrated potent activity against the liver forms of some malaria parasites.

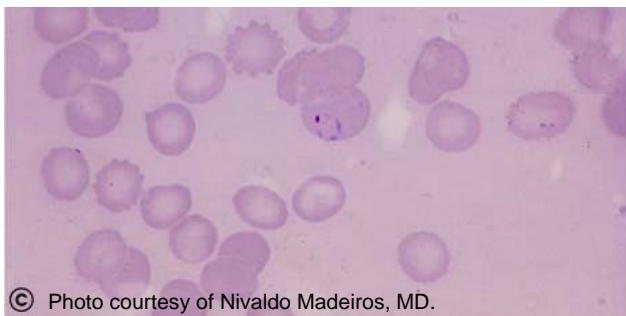
The U.S. Army did further large-scale safety and efficacy studies to develop primaquine beginning in the early 1950's when relapsing malaria due to *P. vivax* emerged as a major problem in returning U.S. veterans from the Korean War. Because service member compliance with chloroquine was adequate in the field, malaria did not become apparent until after cessation of chloroquine when the troops departed Korea. Dr. Alf Alving at the University of Chicago led a research team under contract to the U.S. Army which evaluated safety, toxicity, and efficacy of new antimalarial agents. Volunteers were

recruited from inmates of the Illinois State Penitentiary at Stateville in Joliet, Illinois for these studies. Primaquine was found to kill liver malaria parasites caused by two types of human malaria (*P. vivax* and *P. ovale*) before these are released into the blood stream weeks to months after primary infection, and therefore the drug can cure relapsing malaria. The relatively short half-life (4-6 hours) of primaquine requires daily administration for 14 days to achieve a cure. During the Korean war, primaquine was given as directly observed therapy daily during the 14 day voyage from Korea to the United States. Fortunately, primaquine was shown not to aggravate the problem of seasickness. At the time of FDA licensure, it was known that the dose of 15 mg/day would not be sufficient to cure all strains of *P. vivax* (such as the Chesson strain), but higher doses were associated with hemolytic anemia in persons of African descent.

Subsequently, it became known that doses of primaquine above 15 mg a day can cause anemia due to break-up of blood cells in persons with a genetic defect known as glucose-6-phosphate dehydrogenase deficiency. It is therefore necessary to test for G6PD deficiency if doses larger than 15 mg of primaquine/day are used. This enzyme deficiency is most common in persons of African, Mediterranean, Middle Eastern and southeast Asian descent. The current recommendation of 30 mg/day x 14 days for treatment of *P. vivax* infections therefore is not caused by continuing emergence of primaquine-resistant *P. vivax*.

In recent years a multidisciplinary working group from the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Institute (NMRI) reviewed the existing data on primaquine to determine whether primaquine could be useful as a prophylactic drug, and the Navy laboratory in Jakarta has completed a pivotal Phase III study. The U.S. Centers for Disease Control and Prevention now recommends primaquine as a chemoprophylactic agent option to prevent malaria when other antimalarial drugs cannot be administered.

Tafenoquine (WR 238605), an 8-aminoquinoline analog of primaquine with a half-life of 2-3 weeks, is under development and is expected to be effective both for preventing and treating *P. falciparum* and *P. vivax* malaria.



© Photo courtesy of Nivaldo Madeiros, MD.

Malaria is a blood infection spread by a bite from a mosquito carrying the malaria parasite. Pictured are blood cells infected with *P. vivax*.

**Primaquine references:**

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# Chloroquine-Primaquine

## Information Paper

*A licensed antimalarial drug developed by DoD and its partners*

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product name:** Chloroquine-primaquine

**Commercial name:** Aralen phosphate with primaquine phosphate

**Application:** Antimalarial drug for treatment of *P. vivax* infection

**Company of manufacture:** Sanofi synthelabo

**Date of U.S. licensure:** December 1969 (combined drug)

**Type of product:**

A combination of chloroquine (4-aminoquinoline) and primaquine

**Reasons for development:** To improve compliance with two-drug treatment for relapsing malaria.

### Role of DoD:

This combination of drugs was used successfully by U.N. troops during the Korean conflict, and was a recommended regimen for returning U.S. veterans from the Korean War as of December 1951. The combination was generally given on ships carrying service members back to the U.S. By 1952 the relapsing malaria problem in returning soldiers had fallen dramatically, because chloroquine controls the blood stages of *P. vivax*, and primaquine kills the latent (liver) stages of *P. vivax*.



However, chloroquine and primaquine were not available in a single tablet until 1969, when regulatory approval of chloroquine-primaquine tablets was the first major accomplishment of the Division of Experimental Therapeutics of the Walter Reed Army Institute of Medical Research (NDA #014860). Chloroquine-primaquine was given to soldiers in Vietnam, but the use of dapsone (a sulfone which can cause adverse reactions involving skin, liver and nerves) was necessitated because of chloroquine-resistant *P. falciparum* malaria. The evident need for new malaria drugs led to the U.S. Army's current malaria drug discovery and development program.

**Current status:** The combination drug is no longer commercially available (perhaps due to the small numbers of persons diagnosed in the U.S. with relapsing malaria at the present time), although each drug component is available separately.



*Relapsing malaria due primarily to *P. vivax* afflicted U.S. service members during World War II and the Korean War. Photo: Korean War Veterans National Memorial, Washington, D.C.*

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# Sulfadoxine-Pyrimethamine Information Paper

*A licensed antimalarial drug developed by DoD & its partners*



**Product name:** Sulfadoxine-Pyrimethamine

**Commercial name:** Fansidar

**Application:** Antimalarial drug for treatment

**Company of manufacture:** Hoffman-LaRoche

**Date of U.S. licensure:** 1983

**Type of product:** folic acid inhibitors

## Reasons for development:

Beginning in 1959, chloroquine-resistant malaria was noted in Columbia (and eventually Thailand and Vietnam). During the U.S. involvement in Vietnam, approximately 81,000 cases of malaria were associated with 1.4 million malarial sick days and 133 deaths. *P. falciparum* parasites resistant to the available antimalarial drugs such as chloroquine-primaquine were encountered. At the same time, use of the residual insecticide DDT was discontinued because of insecticide-resistant mosquitoes and adverse environmental effects.



*Division of Experimental Therapeutics at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland is developing new prophylactic and therapeutic anti-malarial drugs for military use.*

**Role of DoD:** Faced with waning usefulness of existing drugs to treat *falciparum* malaria during the Vietnam War era, the U.S. Army gradually established a malaria research and development program beginning in 1961 to develop new prophylactic and therapeutic drugs for military use. This research was coordinated through the Division of Medicinal Chemistry (later renamed as the Division of Experimental Therapeutics) at the Walter Reed Army Institute of Research (WRAIR) now located in Silver Spring, Maryland. Scientists of the United States Army Antimalarial Drug Development Program explored the effect of combinations of drugs that block folic acid on malaria parasite growth. The antimalarial activity of sulfa drugs has been recognized since the 1940's, and dapsone was a sulfone used for chloroquine-resistant malaria in Vietnam. Use of dapsone was limited



*During the U.S. involvement in Vietnam, an estimated 1.4 million sick-days involving 81,000 infections and 133 fatalities were attributed to malaria.*

by adverse effects afflicting skin, blood, liver and nerves. Folic acid is vital to the synthesis of nucleic acids which are prerequisites for cell multiplication. Compounds that have an anti-folic acid effect inhibit the replication of malaria parasites. Sulfadoxine and pyrimethamine interfere with folic acid synthesis at two different steps in parasite replication, so the combination treatment results in a higher degree of anti-folic acid activity compared to when only one of the drugs is given. Pyrimethamine was first created by Burroughs Wellcome in 1950 during a research effort to develop anticancer agents, and was licensed as an antimalarial drug in Britain in 1951. Pyrimethamine was widely used with chloroquine in the WHO control programs of the 1960's. The Walter Reed Institute Army Institute of Research (WRAIR) was involved in clinical trials and FDA approval for the sulfadoxine-pyrimethamine combination (known by the commercial name of Fansidar) to be used to prevent malaria. However, the drug was licensed in other countries prior to U.S. licensure.

## Current status:

Fansidar is still licensed in the United States. Although effective both as prophylaxis and treatment, the use of Fansidar (particularly as a prophylactic agent) is limited because of infrequent but serious adverse allergic reactions involving skin, liver and blood. However, the drug is still used as treatment in some countries where chloroquine resistance is widespread and where other drugs remain unobtainable for financial reasons. Also, the emergence of resistance to the drugs has somewhat limited the usefulness of Fansidar. Although types of antimalarial drugs other than antifolates have been discovered and invented, the mechanism of action of these other drugs is often less clear.

**Sulfadoxine-Pyrimethamine References:**

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# Mefloquine Information Paper

*A licensed antimalarial drug developed by DoD and its partners*

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product name:** Mefloquine

**Commercial name:** Lariam

**Application:** Antimalarial drug for treatment and prevention

**Date of U.S. licensure:** May 1989

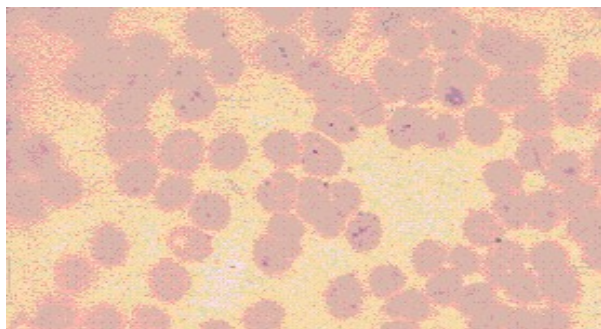
**Type of product:** synthetic 4-quinoline methanol (quinine analog)

**Company of manufacture:** Hoffman-LaRoche

**Reasons for development:** Mefloquine was developed as a treatment/prophylactic for chloroquine-resistant malaria.

## Role of DoD:

The prototype drug for mefloquine was SN 10275, discovered by Americans during the World War II years. The first generation of synthetic quinoline methanols caused unacceptable reactions to skin with sunlight. Mefloquine (WR 149240) was developed by the Division of Experimental Therapeutics at the Walter Army Institute of Research (WRAIR) in the late 1960's by the U.S. Army Medical Research and Development Program in collaboration with the World Health Organization Special Programme for Training and Research in Tropical Diseases (WHO/TDR) and Hoffman-LaRoche, Inc. This division at WRAIR was established in 1961 during the Vietnam War because an increasing burden of malaria was noted among service members. Also, the DoD recognized that there was minimal economic incentive for private pharmaceutical firms to undertake development of antimalarial drugs, since most persons who need such drugs are in developing countries and cannot afford costly pharmaceuticals. The WRAIR program became the lead federal agency for antimalarial drug development, with the expertise and laboratory capability to take a potential antimalarial compound from the chemist's bench through efficacy testing, toxicity testing and clinical trials to licensure by the U.S. Food and Drug Administration (FDA). In recent years, the institute has increasingly formed partnerships with the pharmaceutical industry and WHO and private support groups when possible to help finance and expedite the increasingly expensive and complicated drug development process. No antimalarial has been fully developed by



*P. falciparum malaria parasites can infect red blood cells of all ages, which may result in massive infection.*



*In August 2003 more than 80 of the 290 service members who landed in Liberia were hospitalized because of P. falciparum malaria. The outbreak was blamed on troops' failure to take preventive drugs.*

industry, although industry-government collaborations have yielded new agents. Over 300,000 compounds have been tested for antimalarial activity at WRAIR.

Mefloquine is effective against both *P. vivax* and *P. falciparum*. A very long half-life permits weekly dosing. Surveillance of service members using mefloquine has provided additional information. Although mefloquine was not approved for use in pregnant women during U.S. military operations in Somalia, some female service members who were unaware they were pregnant inadvertently ingested the drug. Follow-up revealed no congenital defects among the infants. Currently mefloquine is recommended as an antimalarial prophylaxis in pregnant women at risk of multidrug-resistant antimalarial infection.

## Current status:

Mefloquine is a relatively low-cost antimalarial, and is still the mainstay antimalarial for the U.S. military. However, the antimalarial action of mefloquine is unknown (as is the case with quinine). Adverse neuropsychiatric effects have been reported, which have a negative impact on compliance. Also, malaria parasites have developed resistance to the drug, especially in southeast Asia and east Africa. The need for new antimalarial drugs is illustrated by the events that occurred during U.S. peacekeeping operations in Africa. Of 290 marines who stepped ashore in Liberia in 2003, 80 developed malaria (28%), and 69(44%) of the 157 who spent at least one night ashore acquired the disease. Five of these malaria-infected marines became extremely ill required intensive care unit support.

**Mefloquine References:**

Palmer KJ, Holliday SM, Brogden RN. Mefloquine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993;45:430-475.

# Quinidine/Quinine Information Paper

Licensed antimalarial drug developed by DoD and its partners

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product Name:** Quinidine gluconate

**Commercial name:** same

**Application:** treatment of chloroquine-resistant *P. falciparum*

**Date of U.S. labeling revision:** 1991

**Type of product:** quinoline methanol, a dextrostereoisomer of the naturally-occurring compound quinine

**Company of manufacture:** Lilly

**Reasons for development:** Malaria is an acute and chronic disease caused by obligate intracellular protozoa of the genus *Plasmodium*. The four species that cause human malaria (*P. malariae*, *P. vivax*, *P. falciparum* and *P. ovale*) are transmitted to humans via the bite of female mosquitoes of the genus *Anopheles*, usually at night (and less commonly via transfusion of infected red blood cells). The clinical course of malaria is characterized by high fever, chills, anemia, and enlargement of the spleen. *P. falciparum* may quickly cause serious or fatal complications (such as brain infection), and *P. vivax* and *P. ovale* can cause relapsing disease. Malaria can quickly decimate troop strength in soldiers lacking immunity to malaria parasites in tropical and some subtropical regions. The disease has had a major impact on several wars involving U.S. troops, including the Spanish-American War, the Pacific Theater in World War II, and the Vietnam War. The availability of prophylactic drug regimens and personal protective measures such as insect repellent and bed nets does not guarantee protection against this disease. Service members may develop malaria after leaving a malarious area because of an inadequate prophylaxis regimen or lack of compliance with this regimen. Most U.S. healthcare providers are not prepared to recognize and treat these infections. Also, because vectors capable of transmitting malaria exist in the United States, malaria in returning troops can be transmitted to other humans.

The compound quinine occurs naturally in the bark of *Cinchona* trees, which were originally found at high altitudes in South America. Peruvian natives chewed on cinchona bark, but probably not for the purpose of treating malaria (which may not have been present in the New World prior to the arrival of Columbus). The drug may originally have been ingested to stop cold-induced tremors in Indians working in Spanish-controlled mines (via a quinine-related direct effect on skeletal muscles and neuromuscular junctions). *Cinchona* bark was introduced into Europe in the early 17th Century as a treatment for fever and malaria by Jesuit priests returning from Peru. Variation of quinine content in different cinchona species led to somewhat inconsistent therapeutic results. In 1820, two young French chemists, Pierre Pelletier and Joseph

Caventou, isolated the alkaloids quinine and chinchonine from cinchona bark. After several French physicians successfully used purified quinine to treat patients with intermittent fever, explorers and scientists began to search for the cinchona species with the highest quinidine content.

**Role of DoD:** Quinine had a profound influence on history, because it enabled missionaries, explorers, colonist and military members to travel and live in many parts of the subtropical and tropical world where malaria was endemic, (which included much of the U.S. until 1951). The drug was commonly used by the U.S. military by 1830. During the Second Seminole War (a war between the Seminole Native Americans attacking settlers in Florida between 1838-1842), Dr. Benjamin Harney, a career army medical officer, demonstrated the efficacy of large doses of quinine to treat remittent fevers. This led to improved results with quinine by military physicians around the globe. During the U.S. Civil War, the Union Army (with members having little or no naturally-acquired immunity to malaria) used over 25,000 kg of quinine or other cinchona products. Quinine was key to the completion of the Panama canal, because use of this drug prevented malaria illness in canal workers. Efforts to synthesize quinine were initiated in 1856 by the British chemist William Henry Perkins, but this goal was not accomplished until 1944 (and has never been achieved on a commercially economic scale). Charles Ledger and Manuel Incra Mamani found a variety of cinchona (*Chinchona ledgeriana*) with a high quinine content in South America, and sold seeds of this tree to the Dutch government in 1865 after the British rejected the offer. Within a short time, the Dutch plantations of Java were producing 97% of the world's supply of quinine (about 10 million kilograms a year by the 1930's). Quinine was eventually licensed in the U.S. as an oral drug after the U.S. FDA was created, but an intravenous form of quinine was never licensed.

Quinidine, the dextrostereoisomer form of quinine, was used as a treatment for cardiac rhythm problems, and the intravenous formulation was later noted to be a life-saving remedy for severe malaria (ironically, the drug must be given in intensive care unit settings because of cardiotoxicity). Intravenous quinidine is currently the only licensed drug for treatment of severe *P. falciparum* malaria available to U.S. service members or civilians. The Walter Reed Army Institute of Research (WRAIR) is now focused on the development of an FDA-approved new drug for the treatment of severe malaria that will replace quinidine. Human trials of the leading candidate -- an intravenous form of artemisinin -- a natural antimalarial which has been used for thousands of years in China -- will begin in May 2005.

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Anonymous. Treatment with quinidine gluconate of persons with severe plasmodium falciparum infection: discontinuation of parenteral quinine. MMWR 40 (RR-4); 21-23, April 19, 1991.

# Doxycycline Information Paper

Licensed antimalarial drug developed by DoD and its partners

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product Name:** Doxycycline

**Commercial name:** Vibramycin

**Application:** Anti-malarial drug for prophylaxis

**Date of U.S. licensure:** New indication approved  
December 1992

**Type of product:** long-acting tetracycline

**Company of manufacture:** Pfizer

**Reasons for development:** Doxycycline -- originally developed as an antibacterial agent -- was found to have slow-acting antimalarial action against tissue malaria parasite forms relating to binding of doxycycline to malaria ribosomes, thereby inhibiting malaria protein synthesis. (Erythromycin and azithromycin -- a modern erythromycin analog -- also inhibit malarial mitochondrial protein synthesis.)



Doxycycline was developed as an antimalarial agent because of (1) resistance to the effective action of mefloquine (initially effective against all chloroquine-resistant *P. falciparum* strains) especially noted in Southeast Asia; (2) adverse effects associated with the use of mefloquine.



## Role of DoD:

The Walter Reed Army Institute of Research (WRAIR) conducted Phase 2 challenge and clinical trials for doxycycline in Thailand, and obtained FDA approval for doxycycline as prophylaxis for both *Plasmodium falciparum* and *P. vivax* malaria.

From June 1992 to November 1993, three Dutch military units served in western Cambodia under the United Nations Transitional Authority. Air Force physicians advised doxycycline for malaria prophylaxis because of concerns that mefloquine had neurological effects that interfered with piloting skills. Of more than 2,000 personnel treated with doxycycline, only 59 developed malaria.

Although doxycycline is a valuable preventative antimalarial agent, the drug requires daily administration and may cause phototoxicity, gut discomfort and diarrhea, all of which impact negatively on compliance. Further, the drug cannot be given to pregnant women and children because it can cause tooth discoloration in developing teeth. Quinine and doxycycline have an additive effect when combined and this combination is used for treatment of *P. falciparum*. Clindamycin is frequently used in place of doxycycline and combined with quinine to treat *P. falciparum* malaria in pregnant women and children.

**Doxycycline references:**

Pang L, Limsomwong N, Singharaj P: Prophylactic treatment of vivax and falciparum malaria with low-dose doxycycline. *J Infect Dis* 1988;158:1124-7.

Pang LW, Limsomwong N, Boudreau EF: Doxycycline prophylaxis for falciparum malaria. *Lancet* 1987; 1:1161-4.

# Halofantrine Information Paper

A licensed antimalarial drug developed by DoD and its partners

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product Name:** Halofantrine

**Commercial name:** Halfan

**Application:** Antimalarial drug for treatment only

**Date of U.S. licensure:** July 1992

**Type of product:** an aminoalcohol, member of the 9-phenanthrenemethanol class (not related to quinine)

**Company of manufacture:** SmithKline Beecham

**Reasons for development:** Halofantrine was developed as a back-up drug to mefloquine to treat chloroquine-resistant *P. falciparum* malaria.

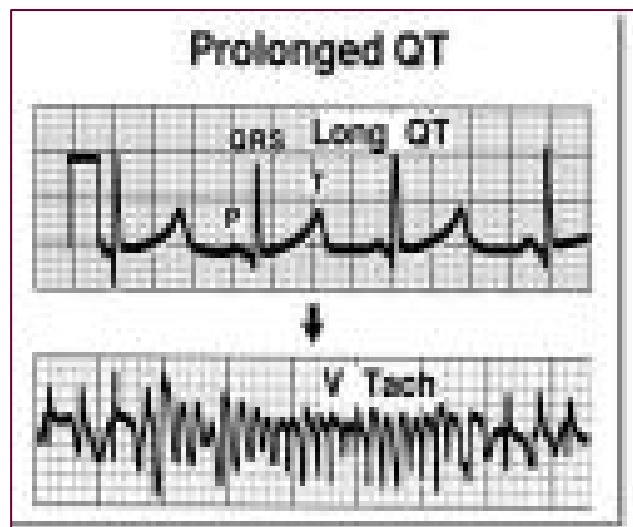
**Role of DoD:** Halofantrine (WR 171669) was developed at WRAIR in collaboration with SmithKline and the World Bank/World Health Organization Special Programme for Training and Research in Tropical Diseases (WHO/TDR) beginning in the late 1960's and early 1970's. Halofantrine was created by replacing the quinoline moiety of the quinoline methanols (quinine-type compounds) by other aromatic groups to form the aryl(amino)carbinols. Of this class of compounds, halofantrine, a 9-phenanthrenemethanol, is the most potent. Commercial development began in the 1980's. The drug is used for treatment of falciparum malaria outside the U.S., but development as a prophylactic drug was stopped over concerns over the short half-life (1-2 days) and adverse effects.



## Current status:

The usefulness of halofantrine is limited by possible cross-resistance with mefloquine, cardiac toxicity, and poor absorption. The drug is no longer licensed in the U.S. because of potential fatal cardiotoxicity related to prolonged QT intervals on electrocardiogram. It is not recommended for use in pregnant or breastfeeding women (the drug is embryotoxic and excreted in breast milk). Absorption is slow but enhanced by fatty foods, but serum levels are unpredictable. The drug is poorly soluble in water, and there is no injectable form of the drug. A micronized formulation was tested and proved promising but was not further developed.

The main metabolite of halofantrine appears to be less toxic and equally efficacious as an antimalarial, but was not developed as a marketable product.



Prolonged QT interval on an EKG strip.

**Halofantrine references:**

Bryson HM, Goa KL. Halofantrine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; 43:236-258.

# Atovaquone-Proguanil Information Paper

*Licensed antimalarial drugs developed by DoD and its partners*

UNITED STATES ARMY MEDICAL RESEARCH  
AND MATERIEL COMMAND



**Product Name:** Atovaquone - Proguanil

**Commercial name:** Malarone

**Application:** Prophylaxis/treatment of falciparum malaria

**Commercial manufacturer:** GlaxoSmithKline

**Date of U.S. licensure:** July 2000

**Type of product:** Malarone is a combination of atovaquone (a 3-substituted-2-hydroxynaphthoquinone) and proguanil (biguanide). These drugs act against blood forms and early liver stage of malaria. Atovaquone (as a single agent) is a hydroxynaphthoquinone currently marketed in the United States under the trade name Mepron for pneumocystis carinii pneumonia, and acts on the malaria parasite by inhibiting the electron transport system at the level of cytochrome bc1 complex, thereby inhibiting pyrimidine biosynthesis, which is essential for Plasmodia (in contrast, mammalian cells are able to salvage pyrimidines). Atovaquone also causes collapse of the parasite mitochondrial membrane potential in *P. falciparum*. The structure of atovaquone differs from that of other antimalarial drugs. Proguanil (Paludrine) which interferes with folic acid synthesis crucial to malaria parasite survival (via binding to the enzyme dihydrofolate reductase in much the same way as pyrimethamine) was developed by the British during World War II, and approved in the U.S. in 1948 for use in malaria. Because proguanil was not widely used in this country, it ceased to be marketed as a single drug in the U.S. in the 1970s. Proguanil is still used overseas as an antimalarial, especially in combination with chloroquine. However, the primary role of proguanil in Malarone may not be as an antifolate. There is demonstrable antimalarial synergy when atovaquone and proguanil are combined, although the mechanism for this enhancement is unclear, and resistance to the antimalarial effect of proguanil alone is common.

**Reasons for development:** (1) Resistance to the effective action of other antimalarial drugs used to prevent malaria is an important clinical problem. (2) Adverse effects have been noted with other antimalarial drugs (photosensitivity, diarrhea with doxycycline, and neurotoxicity with mefloquine).

**Role of DoD:** Development of drug combination strategies, dose-ranging pre-clinical and clinical studies and pivotal efficacy trials were organized by the Walter Reed Army Institute of Research in partnership with GlaxoSmithKline. Early malaria preclinical efficacy testing of atovaquone was conducted at the Walter Reed Army Institute of Research, and subsequent dose-ranging



studies were undertaken at the Armed Forces Research Institute of Medical Science (AFRIMS) in Thailand. In the treatment of acute uncomplicated falciparum malaria, atovaquone proved to be consistently effective in clearing the initial parasitemia. However, unacceptable rates (up to 25%) or recrudescence precluded the further development of atovaquone as monotherapy. Concurrent administration with proguanil, selected for its synergistic activity with atovaquone solidified its role as an antimalarial drug in studies when evaluated at AFRIMS. Subsequent trials were conducted worldwide including WRAIR laboratories in Brazil and in Kenya which demonstrated 99% efficacy for treatment of uncomplicated multidrug-resistant malaria, and 98% efficacy for prophylaxis in placebo-controlled trials. Additional prophylaxis studies have been completed by the NAMRU-2 in Jakarta, Indonesia. Malarone was licensed for treatment of *P. falciparum* malaria in 30 countries, including Australia, prior to U.S. licensure.

## **Current status:**

Malarone has few associated adverse effects other than mild gastrointestinal intolerance, but experience with this drug is relatively limited. This medication is very expensive, and out of economic reach of millions around the world who suffer from malaria. Rapid development of resistance related to spontaneously arising mutations in the parasite that confer drug resistance has been noted when the drug has been used alone as a malaria treatment.

The current status of malaria is worrisome: According to the World Health Organization, there are 300 to 500 million cases of malaria each year resulting in 1.5-2.7 million deaths. Children aged 1-4 are the most vulnerable to infection and death.

**Atovaquone-Proguanil References:**

Anonymous. FDA approves Malarone for the prevention and treatment of malaria. FDA talk paper. July 14, 2000.

De Alencar FEC, Cerutti C, Durlacher RR, et al. Atovaquone and proguanil for the treatment of malaria in Brazil. *Journal of Infectious Diseases* 1997;175:1544-7.